Since the first aortocoronary vein graft implantation was performed in 1967,1 vascular bypass surgery using saphenous vein grafts has become an established therapeutic procedure for patients with ischemic coronary or peripheral arterial diseases. Despite increasing use of arterial grafts in coronary bypass surgery,2 autologous vein remains an important and convenient conduit for surgical revascularization.3 However, vein grafts are associated with poor long-term patencies.4 During the first year after bypass surgery, up to 15% of venous grafts occlude. Between 1 and 6 years, the graft attrition rate is 1% to 2% per year, which increases to 4% between 6 and 10 years after surgery.5 By 10 years, only 60% of vein grafts are patent and only 50% of patent vein grafts are free of significant stenosis.6

Graft occlusion arises either from early thrombosis or from the later onset of graft narrowing.7 After implantation, the vein graft is exposed to immediate increases in flow, shear stress, circumferential stress, radial deformation, and pulsatile stress.6 Progressive thickening of vein grafts, mainly caused by neointima formation in the inner layer, is supposed to be the adaptation of these vessels from the low-pressure venous system to the arterial circulation. Smooth muscle cell (SMC) accumulation,7,8 and matrix biosynthesis by SMCs,9 are key events in the pathogenesis of neointima formation in vein grafts. However, the molecular mechanism of SMC hyperplasia is largely unknown. Consequently, no effective therapy has been established to prevent vein graft failure.

Experimental models of venous bypass graft have been described in dogs,9 rabbits,10 and rats.11 Recent advance in gene-manipulating techniques enables us to produce various genetically modified mice to determine the role of specific molecules in a variety of biological phenomena including vascular remodeling.12–14 Moreover, genetically modified mice harboring marker genes have become available to identify the origin of the cells that contribute to organ remodeling.15–17 Thus, mouse models of vein graft would greatly facilitate genetic analyses of the pathogenesis of neointimal formation. Recent reports described murine models of vein grafts that produced progressive vessel narrowing caused by SMC hyperplasia.18–20

The first evidence for the origin of neointimal cells was provided by Hu et al, who isografted vena cava segment from wild-type mouse to the carotid artery of another mouse that expressed a marker gene, LacZ, in all tissues (ROSA26 mouse).19,21 The authors found that ~40% of SMCs originated from the recipient and 60% from the donor vessel.19 The same group also reported that a large number of endothelial cells in vein grafts underwent apoptosis or necrosis during the first few days and that circulating recipient cells regenerate the endothelium.21 Because it is crucial to identify the exact source of neointimal cells for the development of genetic or pharmacological strategies to prevent vein graft disease,22 the main findings by Hu et al remain to be confirmed by other laboratories.

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Cooley describes a new mouse model of vein graft transplantation.23 The author interpositioned a smaller-diameter graft, a branch of the jugular vein, to the femoral artery. This model has clinical analogy in terms of graft-to-artery diameter match. The grafts were placed into a similar anatomic location as in clinical femoral–popliteal bypass grafting using end-to-end microvascular anastomoses. Compared with other vein graft models of larger species6,10,11 and mice,18,20 the relative neointimal wall thickness was much greater in Cooley’s model, even showing near-occlusive stenosis of the perianastomotic region. However, there was no neointimal formation throughout the arterial graft. Therefore, this graft model seems to be more analogous to human aortocoronary bypass surgery than others. Taking advantage of this model, Cooley investigated the origin of neointimal cells and endothelial cells in vein graft stenotic lesions.23 In contrast to the initial reports by Hu et al,18,19,21 Cooley found that donor-originating cells made a major contribution to neointimal formation. Moreover, the donor-derived endothelial cells also survived and maintained endothelium on the luminal side of the stenotic lesion (Table).

These opposite results apparently result from different experimental systems to test the hypothesis (Figure). In Hu et al’s model,18,19,21 isogeneic vena cava vein was grafted between the 2 ends of the carotid artery by sewing the ends of the vein over the cuffs, over which the carotid arterial ends were turned inside-out. In contrast, Cooley interpositioned a smaller-diameter graft to the femoral artery, using 6 to 10 interrupted stitches of nylon suture per end-to-end anastomosis.23 It is plausible that those differences in surgical procedures significantly influenced the cellular composition of the neointima and endothelium, although both models showed similar neointimal hyperplasia throughout the vein grafts. Consistent with this notion, it was reported that the origin of neointimal cells in transplant-associated arteriosclerosis dif-
Contrasting results from different murine models of vein graft. A, Hu et al\textsuperscript{18,19,21} isografted the vena cava segment from wild-type mouse to the carotid artery of ROSA26 mouse by sleeving the ends of the vein over the cuffs placed at the ends of the carotid artery. In this model, \textasciitilde40\% of SMCs originated from the recipient (shown in blue) and 60\% from the donor vessel (shown in red). Recipient cells also contributed to regeneration of the endothelium. B, Cooley\textsuperscript{23} interpositioned a smaller-diameter venous graft to the femoral artery of ROSA26 mouse using end-to-end microvascular anastomoses. Neointima and endothelium were exclusively composed of donor-originating cells (shown in red).
ffered among different allograft models. Moreover, we reported that recruitment of bone marrow-derived cells to vascular lesions depends largely on the type of vascular injury.26–28

Given the complexity of human vascular lesions, no animal model would represent exact pathophysiology of human autologous vein graft disease. There are many inherent differences between animals and humans in physiological and pathologic responses to mechanical and humoral stimuli. For instance, experimental vein grafts show a characteristic burst of neointimal cell proliferation early after grafting, which leads to a thickened intimal layer by 1 month. This neointimal growth appears to be stabilized beyond 1 to 2 months in most of the animal models, thus differing from the clinical progression of vein graft narrowing. We suggest caution before extrapolating results obtained from an animal model to the pathogenesis of human vein graft stenosis. For better understanding of vein graft disease, we should compare molecular processes of neointima hyperplasia in different models with regard to clinical analogy.

References


3. Mehta D, Izzat MB, Bryan AJ, Angelini GD. Towards the prevention of autologous vein graft disease. There are many inherent differences among different allograft models. Moreover, we reported that recruitment of bone marrow-derived cells to vascular lesions depends largely on the type of vascular injury.26–28

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